C2 8. (amended twice) A method of preventing desulfurization of an aptamer, ribozyme, peptide nucleic acid, or antisense oligonucleotide or bioequivalent thereof comprising combining an oligonucleotide having one or more phosphorothioate linkages with a water-soluble antioxidant in a bi-phasic or multi-phasic formulation.

C3 14. (amended once) The method of claim 8, wherein said oligonucleotide is a ribozyme, aptamer or antisense oligonucleotide.

REMARKS

Claims 1-14 are pending in this application. Claims 1, 8, and 14 have been amended. No new matter has been added.

I. The Claims are Novel.

Claims 1-5, 7-12, and 14 stand rejected under 35 U.S.C. 102(b) as allegedly being anticipated by U.S. Pat. No. 6,258,600 (hereinafter "Zhang"). Applicant traverses the rejection because Zhang does not anticipate the present invention.

At Once Envisage

It has been well established that in order for a genus to anticipate a species under 35 U.S.C. 102, one of ordinary skill in the art must be able to "at once envisage" the species within the generic disclosure. See, for example, *Ex parte A*, 17 U.S.P.Q.2d 1716 (Bd. Pat. App. & Inter. 1990). One of ordinary skill in the art must be able to, for example, write the name of each of the species included in the genus before any of the species can be "at once envisaged." See also *In re Meyer*, 599 F.2d 1026, 1031, 202 U.S.P.Q. 175, 179 (C.C.P.A.1979) which finds that a prior art genus does not "identically disclose or describe, within the meaning of 102" the claimed species "since the genus would include an untold number of species." While these cases refer to chemical species and genera, the concepts therein are applicable to the presently claimed formulations and compositions. For example, in order to anticipate a claimed formulation, that formulation must be capable of being "at once envisaged" by one skilled in the art from a broad genus of formulations.

The formulations of the present invention are not anticipated by Zhang because one skilled in the art could not "at once envisage" a formulation corresponding to the claimed invention from among the myriad of formulations reported in Zhang. The formulations of Zhang are numerous and diverse, the broad description of which constitutes a large portion of the patent (e.g., column 12 to column 24). Within this broad disclosure, literally thousands of different formulations are proposed. For example, formulations include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, powders, granules, suspensions, solutions, foams, and emulsions. Each of these formulations can, for example, include one or more additives such as thickeners, flavoring agents, diluents, emulsifiers, dispersing aids, binders, buffers, permeation enhancers, carriers, etc. Each of the additives encompasses numerous further possibilities, many of which are listed. For example, different excipients (water, salt, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone, etc.), penetration enhancers (surfactants, fatty acids, bile salts, chelating agents, non-chelating non-surfactant), and vesicles (e.g., liposomes, transferomes, etc.) are further stated to be useful in formulations. One can hardly count the number of possible combinations proposed, let alone "envisage" each possibility. Indeed, when one considers only the emulsion formulations of Zhang, the combination of one or more emulsifiers, stabilizers, dyes, anti-oxidants, non-emulsifying materials, and preservatives can make more than 50 different emulsion compositions - and this calculation does not include many of the other reported possible Zhang formulation components.

The amended claims recite formulations and methods involving oligonucleotides [or bioequivalents thereof] *having one or more phosphorothioate linkages*, and *a water soluble antioxidant capable of inhibiting desulfurization of the oligonucleotide*. Zhang does not point one of skill in the art to this combination. Indeed, it appears that in making the present rejection, the Office Action has improperly picked a specific formulation combination in relation to the oligonucleotide component of the present formulations from among innumerable Zhang combinations, and then further (and also improperly) picked phosphorothioate modifications from among an immense number of possible backbone modifications reported in Zhang (see, e.g., column 6 to column 10). These modified oligonucleotide backbone possibilities include phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphorotriesters,

aminoalkylphosphotriesters, alkyl phosphonates, phosphinates, phosphoramidates, thionophosphoramidates, thionoalkylphosphonates, boranophosphates, morpholino linkages, siloxane backbones, sulfide backbones, sulfoxide backbones, sulfone backbones, formetyl, thioformacetyl, methylene formacetyl, methylene thioformacetyl, alkene, sulfamate, methyleneimino, methylene hydrazino, sulfonate, sulfonamide, and amide backbones, to name a few. In addition, myriad sugar and base modifications are also listed (col. 7, line 49 to col. 9, line 15) that can be combined in countless ways with the above-listed backbones.

The Office Action appears to incorrectly suggest that the genus of formulations of Zhang is limited to six emulsions corresponding to the six listed antioxidants. The genus is, in fact, much larger than six. The formulations of Zhang can be analogized to a chemical formula with multiple variables where each variable is connected in turn to a different variable group, each of which can be substituted with additional variables connected to further groups. For example, Zhang formulations on the most general level are represented by a group including, for example, transdermal patch, ointment, lotion, cream, gel, drops, suppositories, sprays, liquids, powders, granules, suspensions, solutions, and emulsions. Then each of these members of these groups carries additional variables represented by further groups. For example, a solution formulation may further include one or more components containing, for example, thickeners, flavoring agents, diluents, emulsifiers, dispersing aids, and binders. Alternatively, emulsion formulations can further include one or more components of the Markush group including emulsifiers (synthetic surfactants, naturally occurring emulsifiers, absorption bases, finely dispersed solids, etc.), stabilizers, dyes, preservatives (methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, boric acid, etc.). Accordingly, the genus of formulations in Zhang is much larger than the Office Action asserts, and is indeed too large to "at once envisage" each of the possible formula species. Accordingly, Zhang does not anticipate the present invention.

Impermissible Picking, Choosing, and Combining

To anticipate, a reference must "clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] ***without any need for picking, choosing and combining various disclosures*** not directly related to each other by the teachings

of the cited references." (emphasis added) *Akzo v. U.S.I.T.C.*, 808 F.2d 1471, 1480 (Fed. Cir. 1986) (citing *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972)); *In re Schaumann* 572 F.2d 312, 314 (C.C.P.A. 1978) ("By having to select [a variable] from among the many possibilities which R in the structural formula [of the reference] may be,... does not give rise to the claimed compound being fully anticipated by the reference.").

As discussed in Applicant's prior response, the Office Action has engaged in impermissible "picking, choosing, and combining" the various ingredients listed in Zhang. Again, Zhang lists a number of different oligonucleotide modifications, modes of administration, and formulation ingredients. Zhang provides ***no direction whatsoever*** to the skilled artisan to choose the specific combination that would yield the presently claimed subject matter, and the Office Action has pointed to no reason at all why those of skill in the art would make such a choice. It is settled law that for a reference to anticipate a claim, it must place the claimed invention in possession of the public. It simply is not legally sufficient that a reference merely recites isolated elements of the claims. See, e.g., *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972). In the present case, the Office Action has not identified any disclosure that would lead those of skill in the art to "envisage" or "clearly and unequivocally disclose" the claimed compositions, as is required by the patent laws. *Akzo v. U.S.I.T.C.*, 808 F.2d 1471, 1480 (Fed. Cir. 1986); *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972)); *In re Schaumann* 572 F.2d 312, 314 (C.C.P.A. 1978). Accordingly Zhang does not anticipate the present claims.

In further support of alleged anticipation of the claims by Zhang, the Advisory Action refers to *In re Sivaramakrishnan*, 673 F.2d 1383, 213 U.S.P.Q. 441 (C.C.P.A.) 1982) ("Sivaramakrishnan case," a copy of which is enclosed herewith) where claims to a polycarbonate resin containing a cadmium laurate additive were found to be anticipated by a reference ("Gable") disclosing a polycarbonate resin containing a metallic salt where numerous example metallic salts, including cadmium laurate, were listed. However, as is pointed out in the Sivaramakrishnan case, Gable discloses a chemical mixture of ***only*** two ingredients, polycarbonate and a metallic salt. In contrast, the Zhang reference reports a chemical mixture (e.g., pharmaceutical formulation) containing any number of ingredients selected from literally pages of unrelated species. Thus, the facts of Sivaramakrishnan case are not analogous to the present subject matter and do not support the present rejection.

Because one skilled in the art could not "at once envisage" from Zhang the claimed formulations, and the Office Action has engaged in impermissible "picking, choosing, and combining," Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. 102(b).

II. The Claims are Not Obvious.

Claims 1-14 stand rejected under 35 U.S.C. 103(a) as allegedly being obvious over U.S. Pat. No. 6,017,545 (hereinafter "Modi") in view of Zhang, U.S. Pat. No. 5,525,621 (hereinafter "Burt"), and U.S. Pat. No. 5,801, 154 (hereinafter "Baracchini"). Applicant respectfully traverses the rejection because the Office Action has failed to set forth a *prima facie* case of obviousness.

To establish *prima facie* obviousness, there must be some suggestion or motivation to modify a reference or combine reference teachings. See, e.g., *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). The Office Action fails to point to legally sufficient motivation for modifying the teachings of Modi, or combining the cited references, to produce the present invention. For example, there is no motivation to select the ONE water-soluble antioxidant over the others listed in Modi to produce the present invention. In fact, none of Modi, Zhang, Burt, or Barachini teach or suggest use of a **water-soluble** antioxidant over other antioxidants. The mere possibility that one skilled in the art **can** use a water-soluble antioxidant is insufficient reason for establishing motivation. See, *e.g.*, *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990).

It is settled law that he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. The Office Action appears to incorrectly assert that motivation arises because Modi states that "it is usual to add at least one antioxidant." However, this statement in Modi fails to provide sufficient motivation to modify the reference or combine references to produce the present invention because it **fails to suggest the selection of a water-soluble antioxidant** over the other non-water-soluble antioxidants.

Moreover, the Office Action improperly fails to point to legally sufficient motivation that would lead one skilled in the art to combine the teachings of Zhang, and Baracchini, and Modi to produce an oligonucleotide having one or more phosphorothioate linkages. When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965)(it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art). It appears that the Office Action has improperly picked and chosen phosphorothioate modification from among the many possible oligonucleotide modification listed in Zhang and Baracchini, and has failed to point to sufficient reason why one skilled in the art would make such a selection. The Office Action incorrectly asserts that motivation arises because various types of modifications, including 2', base, and sugar modifications, can help increase oligonucleotide permeability, half-life, and resistance to degradation. However, this reason is insufficient to show why one skilled in the art would *select phosphorothioate modification over any other modification.* For example, no motivation or reason is provided that would show why one skilled in the art would choose phosphorothioate over, phosphotriesters, methyl phophonates, short chain alkyl or cycloalkyl intersugar linkages, or short chain heteroatomic or heteroyclic intersugar linkages (Baracchini, col., 6, lines 35-37) or phosphotriesters, aminoalkylphosphotriesters, methyl and other alkylphosphonates, phosphinates, phosphoramidates, thionophosphoramidates, thionoalkylphophonates, and boranophosphates (Zhang, col. 6, lines 36-49). Thus, the Office Action fails to provide sufficient motivation to properly combine the cited references to produce the present invention.

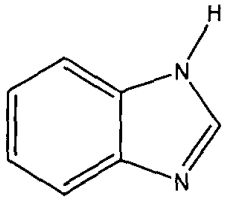
Additionally, in order to establish *prima facie* obviousness, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A.) 1974. In addition to the reasons discussed above, claims 6 and 13 are not obvious because each of Modi, Zhang, Burt, and Baracchini fail to teach the specific antioxidants listed therein. The cited references do not teach cysteine, glutathione, α-lipoic acid, a 2-mercapto-5-benzimidazole salt, or a 2-mercaptoethanesulfonic acid salt as antioxidants. It appears the Office Action incorrectly cites Burt as reporting 2-mercapto-5-benzimidazole salts, however, these compounds

are not taught in this reference or any other cited reference. 2-Mercapto-5-benzimidazole is a benzimidazole derivative having a bicyclic core structure comprised of a benzene fused to an imidazole. A benzimidazole core is shown below. In contrast, the compounds of Burt do not include benzimidazoles because the imidazole moiety is never fused to a benzene. Thus, Burt does not teach or suggest 2-mercapto-5-benzimidazole and the claims are not obvious.

Applicants thank the Examiner for indicating in the Advisory Action mailed March 26, 2003 that Burt does not meet the structural limitations of claims 6 and 13 and that Applicants have overcome the rejection of at least these claims.

Additionally, the Advisory Action incorrectly asserts that the claims are obvious because the prior art clearly discloses that a water soluble antioxidant is a preferred embodiment. Applicants respectfully disagree and can find no statements along these lines in any of the cited references. As discussed above, Modi reports that tocopherol is a preferred antioxidant, however, tocopheral is not a water soluble antioxidant. Accordingly, Applicants maintain that the claims are not obvious.

Because there is no motivation to modify or combine the cited references, and the references fail to teach or suggest all the claim elements, *prima facie* obviousness has not been established. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. 103(a).



benzimidazole

III. The Claims are Supported by Adequate Written Description.

Claims 1-14 were rejected under 35 U.S.C. 112, second paragraph, for alleged lack of written support for the term "bioequivalent," apparently on the basis that the term is sufficiently broad to encompass "anything that specifically binds to any protein or ligand." Final Office Action at page 3. Applicant respectfully traverses the rejection, as the specification provides

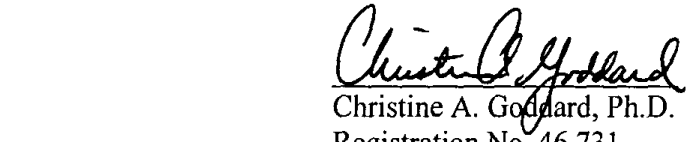
adequate written description for the term on, for example, pages 38-39. Based on the disclosure provided, it would be clear to the art-skilled that a bioequivalent of an oligonucleotide would include, for example, prodrugs, deletion derivatives, conjugates, salts, ribozymes, peptide nucleic acids, and aptamers thereof. Those of skill in the art would understand from these examples what a bioequivalent would be. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. 112, second paragraph.

IV. Conclusion

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claims 1, 8, and 14 according to the marked up versions provided below.

1. (amended twice) A bi-phasic or multiphasic formulation comprising an aptamer, ribozyme, peptide nucleic acid, or antisense oligonucleotide or bioequivalent thereof having one or more phosphorothioate linkages, and a water-soluble anti-oxidant capable of inhibiting desulfurization of said oligonucleotide.

8. (amended twice) A method of preventing desulfurization of an aptamer, ribozyme, peptide nucleic acid, or antisense oligonucleotide or bioequivalent thereof comprising combining an oligonucleotide having one or more phosphorothioate linkages with a water-soluble antioxidant in a bi-phasic or multi-phasic formulation.

14. (amended once) The method of claim 8, wherein said oligonucleotide is a ribozyme, aptamer or antisense [nucleic acid] oligonucleotide.